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10/522,074	07/08/2005	Darrell Sleep	P30,358USA	7594

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EXAMINER	
GUDIBANDE, SATYANARAYAN R	
ART UNIT	**PAPER NUMBER**
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,074	SLEEP, DARRELL	
	Examiner	Art Unit	
	Satyanarayana R. Gudibande	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) *4-7, 9, 11-19 and 26-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,8,10 and 20-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of SEQ ID NO:28 as the species and election of group I invention in the reply filed on 2/22/07 is acknowledged. The traversal arguments were addressed in the office action dated 4/19/07.

The elected species SEQ ID NO: 28 has been found to be free of art. However, upon extending the search, prior art was found on SEQ ID NO: 1.

Claims 1-56 are pending.

Claims 4, 5-7, 9 and 11 have been withdrawn from further consideration as being drawn to non-elected species.

Claims 12-19 and 26-56 have been withdrawn from further consideration as being drawn to non-elected invention.

Claims 1-3, 8, 10 and 20-25 are examined on the merit.

Any rejections or objections made in the previous office action dated 4/19/07 and not specifically mentioned hare are considered as withdrawn.

Withdrawn Rejections

Claim Rejections - 35 USC § 101

Applicant's arguments, see page 17 and 18, filed 10/19/07, with respect to the rejection(s) of claim(s) 1 and 21-25 under non-statutory subject matter have been fully considered and are

persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of the amendments made to claims 1, 21 and 24. The new ground of rejection appears below.

Claim Rejections - 35 USC § 102

Applicant's arguments, see page 22, filed 10/19/07, with respect to the rejection(s) of claim(s) 1, 3, 6, 8, 10 and 20-23 under non-statutory subject matter have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of the amendments made to claims 1, and 21 and in view of new prior art found on SEQ ID NO: 1. The new ground of rejection appears below.

Maintained rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 8, 10 and 20-25 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention as stated in the office action dated 4/19/07 as reiterated below. The rejection

has been modified to reflect the change in the claim numbers that is being examined on the merit in this office action and to reflect the amendments made to claims 1, 21 and 24. Response to applicant's argument appears at the end of the rejection.

In the instant application, applicants claim a polypeptide comprising (i) a leader sequence, the leader sequence comprising (a) a secretion pre sequence, and (b) the following motif: -X1-X2-X3-X4-X5- where XI is phenylalanine, tryptophan, or tyrosine, X2 is isoleucine, leucine, valine, alanine or methionine, X3 is leucine, valine, alanine or methionine, X4 is serine or threonine and X5 is isoleucine, valine, alanine or methionine ; and (ii) a mature desired protein.

The MPEP clearly states that the purpose of the written description is to ensure that the inventor had possession of invention as of the filing date of the application, of the subject matter later claimed by him. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir.1997). The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include, "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from

other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed invention is sufficient" MPEP 2163.

The claims as recited, encompasses not just the peptide motif defined by $-X_1-X_2-X_3-X_4-X_5-$ but it requires the presence of a leader sequence, a secretion pre sequence and a mature desired protein. The claim does not recite the nature of the 'leader sequence', 'pre sequence' or 'the mature desired protein' in terms of the amino acid sequences that would properly define each of these different peptides that constitute the claimed polypeptide sequence. The claims do not adequately provide structural characteristics of 'leader sequence', 'the pre sequence' or 'the mature desired protein' that make up the polypeptide that is claimed in the instant invention. The specification does not provide adequate support to the claims as recited in describing the instantly claimed invention wherein individual components (such as leader sequence, pre sequence and mature desired protein) of the claimed polypeptide. Recitation of terms such as 'leader sequence', 'pre sequence' and 'mature desired protein' without properly identifying the structural characteristics of these molecules with required sequence identification numbers (SEQ ID Nos) or structural characteristics lead to lack of written description according to 35 USC 112 first paragraph.

A mature desired protein sequence is the primary amino acid sequence that will be present in the expression product following post-translational processing by the expression system in which the polypeptide of the invention is expressed. The-desired protein is preferably suitable for secretion from a cell in which the polypeptide of the invention is expressed.

The specification on page 7, lines 3-8 states that, "[A] mature desired protein sequence is the primary amino acid sequence that will be present in the expression product following post-translational processing by the expression system in which the polypeptide of the invention is expressed. The-desired protein is preferably suitable for secretion from a cell in which the polypeptide of the invention is expressed", refers to proteins that are post-translationally modified that are naturally occurring that are secreted from the cells. However, the claim 1 as recited claims a polypeptide comprising of a leader sequence, the leader sequence in turn comprising a secretion pre sequence of motif represented by SEQ ID NO: 1 and a mature desired protein. With the exception of the penta-peptide motif, it is unclear from the claim as recited what is the nature and composition of the leader sequence, the secretion pre sequence and the nature of the mature desired protein in terms of its amino acid sequence that would provide structural aspect to these sequences. In the absence of structural feature that represent the instantly recited polypeptide the claims encompass any and all known and unknown polypeptides that comprises of the motif represented by SEQ ID NO: 1. In addition to this claims 8 and 10 recite "albumin secretion pre sequence or a variant thereof". The term "variant" has been defined very broadly as, "[v]ariant of an albumin pre sequence, as used above, refers to an albumin pre sequence wherein at one or more positions, Other than at those defined by X1, X2, X3, X4 or X5 above, there have been amino acid insertions, deletions, or substitutions, either conservative (as described above) or non-conservative, provided that such changes still allow the peptide to act as a pre sequence" (bridging paragraph of page 8 and 9 of instant specification). The specification as disclosed does not support the innumerable variations possible commensurate with the scope of the definition provided in the specification. The claims 22 and 24 as recite the limitation

"variant thereof" with respect to mature desired protein as "[v]ariant, in the context of a desired protein, refers to a protein wherein at one or more positions there have been amino acid insertions, deletions, or substitutions, either conservative or non-conservative, provided that such changes result in a protein whose basic properties, for example enzymatic activity or receptor binding (type of and specific activity), thermo stability, activity in a certain pH-range (pH-stability) have not significantly, been changed. "Significantly" in this context means that one skilled in the art would say that the properties of the variant may still be different but would not be unobvious over the ones of the original protein" (page 19 of instant specification). The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Thus the broad definition of a variant of an unknown polypeptide wherein the primary structure of the polypeptide itself has not been defined adequately in terms of leader sequence, secretion pre sequence and mature desired protein, a variant of such a polypeptide with a broad definition that provide functional characteristics without structural correlation associated amounts to lack of written description.

According to the specification, only a portion of the cited albumin protein is the polypeptide recited in the instant invention, as the motif as represented by the **penta-peptide** or a **part of the motif** as per claim 20 is not a part of the desired polypeptide. However, the desired polypeptide comprises of the 'leader sequence, 'pre sequence' and 'a mature desired protein'. Therefore, the claims as recited suffer from lack of written description in clearly describing the invention to one skilled in the art. Again, the claims as recited encompass any and all naturally

occurring proteins (polypeptides). The fact that the claim as recited encompass any and all natural polypeptide combined with lack of description in the specification of the individual components such as 'leader sequence', 'pre sequence' and 'a mature desired protein' that constitute each of the desired polypeptide clearly indicates that to one skilled in the relevant art that the inventor(s), at the time the application was filed, may not have had possession of the claimed invention.

Response to arguments

Applicants argue that "written description does not require a description of the complete structure of every species within the chemical genus". Applicants further argue that the terms "leader sequence", "pre sequence" and "a mature desired protein" are easily understandable to a person of ordinary skill in the art. Applicants further try to substantiate their argument with functional definitions for the afore-mentioned terms form cited references of Voet and Voet, cited reference of Gierasch and sections of the instant specification that again provide broad functional definitions of the terms. Applicants also state that, "[A]pplicant submits that the claimed motif variants represent functional modifications to the exemplified motif (FIVSI), in that they allow for the presence of conservative amino acid substitutions at each of the positions of the exemplified motif:

• the first position of the motif, X1, may only be an aromatic amino acid (like the exemplified Phe residue);

• X2, X3, and X5 are selected from groups of amino acids which have non-polar side chains (like the exemplified Ile, Val and Ile residues, respectively);

• X4 may only be either the exemplified Ser residue or its functional equivalent Thr, both of which have hydroxyl group-containing uncharged polar side chains.

It is well established that there is generally a low level of sequence identity between the amino acid sequences of different leader sequences and that their properties as leader sequences are determined by the chemical and steric properties of the component amino acids, rather than their absolute identities. See Gierasch, p. 27 (attached) ("Signal sequences seem likely to interact with many cellular components.., but they apparently do so by virtue of their overall properties (residue type and patterns of residues) as opposed to specific sequence."

Applicant's arguments filed 10/19/07 have been fully considered but they are not persuasive. Because, providing a mere general definition of the terms "leader sequence", "pre sequence" and "a mature desired protein" and just because they are well known in the art does not impart specificity to these terms. As seen in the cited reference of Gierasch, it is clearly stated that, the role of signal sequences are still poorly understood (page 923, paragraph 1), the reference further state that "despite this striking **conservation of a critical cellular function**, signal sequences **display a remarkable lack of primary sequence homology even among closely related proteins**". This clearly illustrates facts that are contrary to applicant's argument that functional definition is sufficient to satisfy the lack of written description in the absence of a structure of the biomolecule to correlate with the function. On page 925, column 2, paragraph 4, Gierasch, further teaches that "comparison of all known signal sequences reveal no regions of strict homology". On page 926, column 1, paragraph 1, Gierasch's reference further state that "many reports of alterations in signal sequences, including point mutations that lead to loss of the

function". This is contrary to the applicant's argument that, "written description does not require a description of the complete structure of every species within the chemical genus". As mentioned earlier, "[T]he MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618".

Therefore, the claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention and hence the rejection under 35 USC 112 first paragraph is proper and maintained.

New grounds of rejections

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1 and 21-25 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 1 as recited encompasses any and all native polypeptide (protein) of nature. Claims 21-25 as recited encompasses again any and all native proteins and in particular human albumin (claim 23) and transferrin (claims 24 and 25). The polypeptide SEQ ID NO: 589 of WO 01/64834 A2 of Tang, et al., discloses the penta peptide motif FIASA (page 133) as shown below:

VGSQGLVPKKNRPAGKDLGAPSGGPPR KCIP/WQGLLLTAS\LLAL*EAPTTAWL**FI**

ASAPYEVAEGENVHLSVVYLRENLYSY GWYKGKTVEPNQLIAAYVIDTHVRTPGP

AYSGRETISPSGDLHFQNVTLEDTGYYN LQVTYRNSQIEQASHLRVYESVAQPSI

QASSCI.

Key to the above protein sequence:

Amino acid sequence (A=Alanine C=Cysteine, D=Aspartic Acid, E=Glutamic Acid, F=Phenylalanine, G=Glycine, H=Histidine, I=Isoleucine, K=Lysine, L=Leucine, M=Methionine, N=Asparagine, P=Proline, Q=Glutamine, R=Arginine, S=Serine, T=Threonine, V=Valine, W=Tryptophan, Y=Tyrosine, X=Unknown, *=Stop codon, /=possible nucleotide deletion, \=possible nucleotide insertion

Response to arguments

Applicants have made a comment on page 17 of the remarks that "it appears that the Examiner is making a more of an anticipation argument".

Applicant's arguments have been note and it should be noted the claim 1 as recited the polypeptide comprises of secretion pre sequence that comprises of a penta-peptide motif. Hence, office cited a reference to show that the penta-peptide motif is found in the peptide disclosed by Tang, et al. It is not an anticipation rejection. Since the claim as recited claims a polypeptide comprising (i) a leader sequence, the leader sequence comprising (a) a secretion pre sequence, and (b) the following motif: -X1-X2-X3-X4-X5- where XI is phenylalanine, tryptophan, or tyrosine, X2 is isoleucine, leucine, valine, alanine or methionine, X3 is leucine, valine, alanine or methionine, X4 is serine or threonine and X5 is isoleucine, valine, alanine or methionine ; and (ii) a mature desired protein, the claim encompasses any and all natural proteins. The amended claims with the recitation of the limitation "a mature desired protein" does not imply that the polypeptide claimed in the claim is not a product of nature. The definition of the "mature protein" as provided in the applicant's remark states that the mature protein is without its pre sequence or pre-pro sequence (bridging paragraph on pages 16 and 17) does not preclude it to be not a product of nature because, the claim as shown above encompass naturally occurring proteins. Therefore, polypeptide as claimed is product of nature.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 8, 20-22 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/64834 A2 of Tang, et al.

Applicants claim a polypeptide comprising (i) a leader sequence, the leader sequence comprising (a) a secretion pre sequence, and (b) the following motif: -X1-X2-X3-X4-X5- where XI is phenylalanine, tryptophan, or tyrosine, X2 is isoleucine, leucine, valine, alanine or methionine, X3 is leucine, valine, alanine or methionine, X4 is serine or threonine and X5 is isoleucine, valine, alanine or methionine ; and (ii) a matured desired protein.

The cited reference of Tang, et al., discloses the motif 'FIASA' in SEQ ID NO: 589 (page 133, 3rd sequence in the table) that corresponds to the Seq ID NO: 1 of the instant application as shown in the sequence listing:

```
<210>   1
<211>   5
<212>   PRT
<213>   Artificial Sequence

<220>
<223>   Synthetic polypeptide leader sequence

<220>
<221>   MISC_FEATURE
<222>   1
<223>   CAN BE EITHER Phe OR Trp OR Tyr

<220>
<221>   MISC_FEATURE
<222>   2
<223>   CAN BE EITHER Ile OR Leu OR Val OR Ala OR Met

<220>
<221>   MISC_FEATURE
<222>   3
<223>   CAN BE EITHER Leu OR Val OR Ala OR Met

<220>
<221>   MISC_FEATURE
<222>   4
<223>   CAN BE EITHER Ser OR Thr

<220>
<221>   MISC_FEATURE
<222>   5
<223>   CAN BE EITHER Ile OR Val OR Ala OR Met

<400>   1
Xaa Xaa Xaa Xaa Xaa
1               5
```

The disclosure of the sequence motif FIASA in the cited reference of Tang, et al., meets the limitations of claims 1-3. The instant claims 8, 20-22 and 24 recite a limitation "variant thereof" with reference to albumin secretion pre sequence (claim 8), secretion pre sequence (claim 20), variant or fragment of albumin protein (claim 22) and variant or fragment of transferrin protein (claim 24), since the definition of "variant" has been very broadly as follows: "the term "variant" has been defined very broadly as, "[v]ariant of an albumin pre sequence, as used above, refers to an albumin pre sequence wherein at one or more positions, Other than at those defined by X1, X2, X3, X4 or X5 above, there have been amino acid insertions, deletions, or substitutions, either conservative (as described above) or non-conservative, provided that such changes still allow the peptide to act as a pre sequence" (bridging paragraph of page 8 and 9 of instant specification). ""[V]ariant", in the context of a desired protein, refers to a protein wherein at one or more positions there have been amino acid insertions, deletions, or substitutions, either conservative or non-conservative, provided that such changes result in a protein whose basic properties, for example enzymatic activity or receptor binding (type of and specific activity), thermo stability, activity in a certain pH-range (pH-stability) have not significantly, been changed. "Significantly" in this context means that one skilled in the art would say that the properties of the variant may still be different but would not be unobvious over the ones of the original protein" (page 19 of instant specification). The definition of the "variant thereof" of the instant specification reads on the protein sequence SEQ ID NO: 589 of the cited reference of Tang, et al. This meets the limitations of claims 20-22 and 24. Hence, the cited reference of Tang, et al., anticipates the instant invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Satyanarayana R. Gudibande, Ph.D.
Art Unit 1654

1/4/09
ANISH GUPTA
PRIMARY EXAMINER